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Review

# Macrophages and fibrosis: How resident and infiltrating mononuclear phagocytes orchestrate all phases of tissue injury and repair☆

Maciej Lech *, Hans-Joachim Anders

*Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians Universität München, Germany*

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ABSTRACT

Certain macrophage phenotypes contribute to tissue fibrosis, but why? Tissues host resident mononuclear phagocytes for their support to maintain homeostasis. Upon injury the changing tissue microenvironment alters their phenotype and primes infiltrating monocytes toward pro-inflammatory macrophages. Several mechanisms contribute to their deactivation and macrophage priming toward anti-inflammatory and pro-regenerative macrophages that produce multiple cytokines that display immunosuppressive as well as pro-regeneratory effects, such as IL-10 and TGF-beta1. Insufficient parenchymal repair creates a tissue microenvironment that becomes dominated by multiple growth factors that promote the pro-fibrotic macrophage phenotype that itself produces large amounts of such growth factors that further support fibrogenesis. However, the contribution of resident mononuclear phagocytes to physiological extracellular matrix turnover implies also their fibrolytic effects in the late stage of tissue scaring. Fibrolytic macrophages break down fibrous tissue, but their phenotypic characteristics remain to be described in more detail. Together, macrophages contribute to tissue fibrosis because the changing tissue environments prime them to assist and orchestrate all phases of tissue injury and repair. This article is part of a Special Issue entitled: Fibrosis: Translation of basic research to human disease.

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## 1. Introduction

Fibrogenesis has been maintained throughout evolution because of its live-saving benefits during the wound healing processes that occur after injury. On the other hand fibrogenesis contributes to many chronic progressive disease states.

In general, any kind of injury involves a sequence of responses to control the injurious trigger that restore homeostasis [1]. Tissue loss, either by trauma or by the collateral damage during the inflammatory phase, requires tissue repair, which involves scaring. Cells of the monocyte/macrophage lineage are central players of the immune response following tissue damage. Macrophages have many functions, including the promotion and resolution of inflammation, the removal of apoptotic cells, and the support of cell proliferation following injury. Macrophages exist in several different phenotypic states within the injured tissue and promote inflammation and at the same time are beneficial for the repair of healing tissue.

In this review, we will summarize how mononuclear phagocytes, especially macrophages, are involved in the various stages of tissue injury and repair. The different and specific roles of macrophages during parenchymal repair, mesenchymal repair, and fibrolysis become more obvious from the perspective of the tissues' needs to regain homeostasis upon injury.

## 2. Phases of tissue injury and repair

### 2.1. The injury phase

Pathogen entry, toxic or oxidative stress often causes necrotic cell death, which implies the release of damage- and pathogen-associated molecular patterns (DAMPs or PAMPs) released by necrotic cells and/or microorganisms, respectively. These have an identical capacity to activate toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors (CLRs) or inflammasomes for the secretion of cytokines and chemokines, which set up tissue inflammation and leukocyte recruitment [2–6]. The associated immunopathology often largely contributes to acute impairment of tissue dysfunction or mortality, e.g. in sepsis, pneumonia, meningitis, or acute kidney injury. The antimicrobial activity of recruited immune cells involves reactive oxygen species production, enzyme and pro-inflammatory cytokine release. Furthermore, a persistent accumulation of immune cells may prolong tissue inflammation and aggravate immunopathology.

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* Corresponding author at: Medizinische Klinik und Poliklinik IV, Klinikum der Universität München - Innenstadt, Schillerstr. 42, 80336 München, Germany. Tel.: +49 89 218075855; fax: +49 89 218075860.
*E-mail address:* maciej.lech@med.uni-muenchen.de (M. Lech).

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### 2.2. Resolution of inflammation upon control of the injurious trigger

Mechanisms that control inflammatory processes and restore homeostasis are crucial for efficient recovery and preserving tissue morphology and function [7]. Inflammation suppresses tissue repair, which implies that the resolution of inflammation is necessary to tip the balance to parenchymal repair and healing. One of the events participating in these changes is the decreasing amount of DAMPs and PAMPs and the high number of apoptotic neutrophils that need to be removed by macrophages. This process not only turns pro-inflammatory into anti-inflammatory macrophages that secrete large amounts of IL-10 and TGF-β [8,9], but the sequential activation of transcription factors either also promotes inflammation such as NF-κB [10] and IRF-1 [11] and subsequently its resolution like IRF-4 [12,13].

### 2.3. The epithelial and vascular repair phase

Restoring tissue integrity after any kind of injury may be achieved by proliferation of 1. surviving cells, 2. local progenitor cells, and 3. bone marrow-derived precursors [14,15]. The capacity for tissue regeneration varies between different organs. While blood cells easily and completely regenerate from hematopoietic stem cells inside the bone marrow the capacity of vascular regeneration, again from endothelial progenitors inside the bone marrow, is already somewhat limited, especially in chronic disease states, like uremia [16–18]. Remote cellular compartments in solid organs may not even be accessible to bone marrow-derived stem cells even though these still promote repair by paracrine secretion of growth factors [19]. Therefore, especially epithelial structures, like the epidermis, the intestinal epithelium and renal podocytes or tubular epithelial cells rely on local committed progenitor cells for repair [15,20].

### 2.4. Mesenchymal repair

Fibrotic tissue seals and mechanically stabilizes the “wound” only when damage is not limited to the epithelium and/or repair is not fast enough [21]. This may involve partial loss of organ function also because fibrosis involves sclerosis that e.g. functionally restricts the flexibility of skin/joints/small bowel; affects electric circuits and hemodynamics in the heart; reduces arteriolar compliance followed by arterial hypertension or causes persistent proteinuria from the renal glomeruli. Cellular and molecular events in mesenchymal healing (fibrosis) include 1. infiltration of immune cells and fibrocytes, 2. accumulation of extracellular matrix (ECM), 3. activation of fibroblasts and myofibroblasts, and 4. angiogenesis [22]. Fibrosis is often associated with persistent inflammation and loss of organ function, i.e. chronic disease [23]. Their causal relationship is often anticipated but remains unclear [24].

### 2.5. Minimizing scars

Extracellular matrix (ECM) turnover during homeostasis already implies that interstitial cells release proteases and that phagocytes remove ECM breakdown products [25]. Scars shrink by reducing excess ECM via enzymatic activity, e.g. by matrix metalloproteases (MMP). Factors that limit fibrogenesis and promote fibrolysis are prostaglandin E2 [26] or caveolin-1 and BMP7 [27,28]. Furthermore, recombinant TGF-β3 application in humans' skin injury supports ECM breakdown and scarless healing [29]. TGF-β3 application prevents excessive proliferation of myofibroblasts and changes their migration toward a pattern normally seen only in the fetal stage where scarless healing occurs [29].

## 3. Origin and diversity of monocytic phagocytes in healthy tissues

Macrophage development is controlled by CSF-1R, also known as macrophage colony-stimulating factor-1 receptor, which is expressed on all monocyte progenitors [30]. Ligation of this receptor activates the myeloid developmental regulator PU.1. Mice deficient in CSF-1R or its ligand do not develop any monocyte, macrophages or dendritic cells [31]. Other essential factors responsible for the development of myeloid cells include IRF8, KLF4, c-Maf and many more molecules, which function have not been precisely described yet [30]. The phenotype of circulating monocytes significantly differs in terms of their response to infection and inflammation [32]. Monocytes circulate in blood and migrate into tissues where they mature and develop into macrophages. Human monocytes consist of three subsets which appear to be responsible for different processes. The new classification of monocytes is based on the expression of CD14/CD16 and Ly6C/CD43 in human and mice respectively [32]. CD14++CD16− (in mice Ly6C++CD43+) monocytes are commonly referred to as the ‘classical monocytes’ which produce high levels of TNF-α and MHC II [33] and are the major population of human monocytes. They also express CCR2 and, therefore, respond to CCL2 for transendothelial migration and secretion of additional pro-inflammatory cytokines [34,35]. Most of these circulating monocytes become pro-inflammatory tissue macrophages once they exit the vasculature. By contrast ‘nonclassical’ CD14+CD16++ monocytes (in mice Ly6C+CD43++) and ‘intermediate’ monocytes (CD14++CD16+ subsets in humans and Ly6C++CD43− in mice) are in the minor population. The ‘intermediate’ subset expresses surface markers at levels between ‘classical’ and ‘nonclassical’ subsets [36–38]. ‘Nonclassical’ monocytes were shown to response poorly to LPS but still are able to produce TNF-α. By contrast CD14++CD16+ ‘intermediate’ monocytes show high expression of TLR4, increased phagocytic activity and decreased antigen presentation. By contrast LPS-stimulated CD14++CD16+ monocytes produced more IL-10 than ‘nonclassical’ monocytes and showed anti-inflammatory functions [39]. This heterogeneity of mononuclear phagocytes in healthy or injured tissues relates to different microenvironments in different tissue compartments that also undergo changes during the different phases of dynamic disease processes, which then is associated with shifts toward different monocytic phagocyte populations. This phenotype plasticity is the reason why most of the in vivo studies failed to reveal pure macrophage clusters of a single phenotype [40–42]. A detailed discussion of classifying macrophages by their surface marker expression profiles has been provided elsewhere [41–44]. In vivo, macrophages are present in all tissues and participate in maintaining homeostasis. For example, the lung and liver are exposed to pathogens from the air or pathogen components from the intestines, respectively, which explain the predominance of macrophages that can clear pathogen components by phagocytosis. Also the bone marrow requires macrophages for the clearance of the nuclei expelled from erythroblasts [45]. The intestinal mucosa rather hosts dendritic cells that pick up signals from the microbiota to secrete mitogenic mediators that support the maintenance of the intact epithelial lining [46]. Sterile organs rather harbor dendritic cells that process autoantigens and send tolerogenic signals to lymphocytes in regional lymphnodes as a mechanism of peripheral tolerance [47,48].

Together, already during homeostasis different organs provide unique microenvironments, which generate different shapes and functional properties of their resident mononuclear phagocytes, e.g. resident dendritic cells or rather resident tissue macrophages. Tissue injuries suddenly change the organ-specific environment, which, depending of the type of injury, leads to adaptive changes of the resident mononuclear phagocytes as well as of the infiltrating monocytes.

## 4. Monocytic phagocytes in the tissue injury/inflammation phase

PAMPs and DAMPs are responsible for generating pro-inflammatory macrophage subsets during infections and sterile tissue injury, respectively, because they activate pattern-recognition receptors on the macrophage surface [4–6]. These macrophages secrete pro-inflammatory

cytokines and chemokines and attract other immune cells such as neutrophils or natural killer cells [49,50]. Furthermore, such activated macrophages have the ability to kill intracellular bacteria and have a phenotype proposed by in vitro studies as M1 macrophages (Fig. 1, Table 1). M1a macrophages were defined by IFN-γ and LPS stimulation, whereas M1b macrophages by stimulation with PAMPs. Generally, inflammatory M1a macrophages secrete IL-1, IL-12, IL-23, tumor necrosis factor (TNF)-α and reactive oxygen species. They express high levels of inducible nitric oxide synthase, major histocompatibility complex class II ($MHCII^{high}$) and IL-1R [42]. They have enhanced phago- and endocytic abilities and increased expression of co-receptors required for antigen presentation but cannot efficiently ingest apoptotic cells. This bactericidal macrophage phenotype appears in the early phases of tissue injury shortly to enforce local host defense against pathogens, a process that is potentially life-saving during infections but also causes collateral tissue damage [42,51,52]. However, sterile injuries induce inflammation similar to injury caused by pathogens [42,51,52]. M1b macrophages which predominantly develop in these conditions have been described to being activated after endogenous danger signals, such as HMGB1, iron, histones or ATP, ligate pattern recognition receptors [42,51–53]. Such sterile injuries can occur in many organs [54–56]. Although inflammation plays an important function in limiting the numbers of pathogens, it limits also the epithelial healing and induces tissue damage and dysfunction. This finding was supported by showing an improved re-epithelialization of sterile wounds in *PU.1*-deficient mice that lack neutrophils and macrophages, or in *Myd88*-deficient mice that have impaired innate immune responses [57–59]. Additionally, reactive oxygen species or TNF-α was shown to promote cell cycle arrest or apoptosis in epithelial and endothelial cells. A persistent pro-inflammatory macrophage phenotype is sufficient to turn acute into chronic tissue inflammation and progressive loss of tissue [60]. Classically-activated pro-inflammatory macrophages amplify inflammation and loss of parenchymal cells also in a variety of kidney diseases such as in anti-glomerular basement membrane glomerulonephritis [61], lupus nephritis [62–67], antigen-induced immune complex glomerulonephritis [68], renal allograft injury [69], ischemia reperfusion injury [70–73], and adriamycin nephropathy [74]. Blocking the recruitment and activation of M1 macrophages reduces immunopathology in a number of inflammatory kidney disease models [75–77]. These observations do not only apply to the kidney, but also to autoimmune diseases of the central nervous system [78,79], CCl4-induced liver injury and several other infectious and noninfectious types of inflammation in solid organs [7,80]. However, some studies also document that wound closure is significantly delayed upon early macrophage depletion [81].

Also in sterile wounds the depletion of pro-inflammatory macrophages leads to reduced scar areas [81], but in sterile environments the inflammatory phase is short-lasting. Therefore, sterile wounds heal faster [14,82]. This is also because immunomodulatory elements rapidly downregulate the inflammatory response and promote tissue repair [83]. It is of note that certain macrophage phenotypes contribute to this anti-inflammatory and pro-regeneratory phase of tissue injury and repair.

## 5. Monocytic phagocytes during the resolution of inflammation

The sequential influx of neutrophils and macrophages upon injury is a hallmark of acute tissue damage. Macrophages are needed to remove those neutrophils that undergo NETosis or apoptosis (Fig. 1) [84]. The phagocytosis of apoptotic cells is a central element that changes the phenotype of pro-inflammatory macrophages into anti-inflammatory macrophages and subsequently promotes the resolution of inflammation [85,86]. This 'waste elimination process' avoids persistent exposure of immunostimulatory elements to immune cells. Furthermore, such alternatively-activated macrophages release mediators such as IL-4, IL-13, IL-10 or transforming growth factor-β1 (TGF-β1) that rather shift tissue inflammation toward tissue repair [8,9,87]. A key regulator of these processes may be circulating serum amyloid P also known as pentraxin-2 (PTX-2), which opsonizes dead

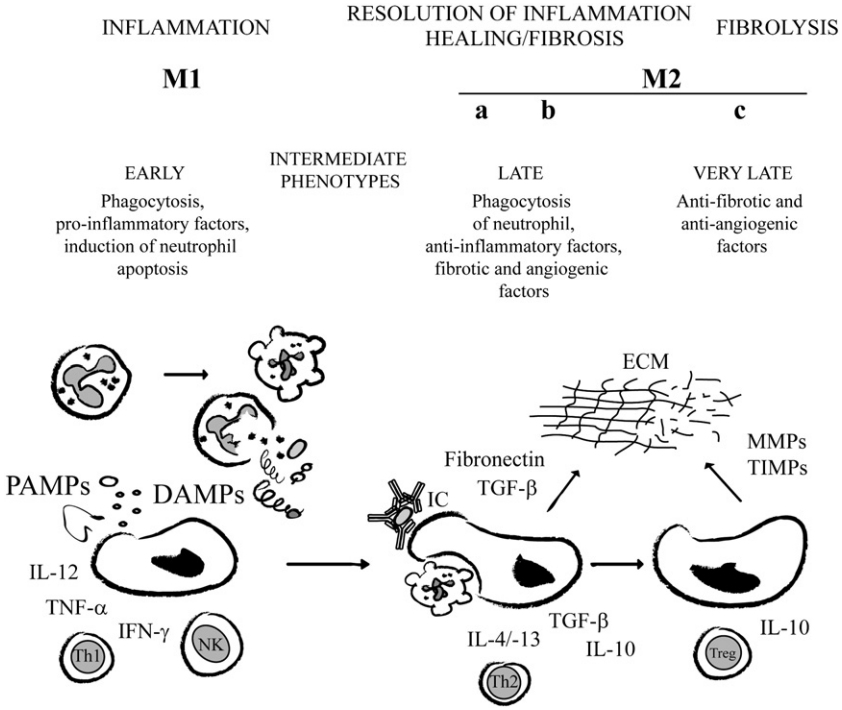


**Fig. 1.** Macrophages and renal fibrosis. Tissue damage activates parenchymal cells, which results in subsequent activation of innate immunity. This includes the recruitment of monocytes that differentiate into various macrophage phenotypes depending on the local tissue environment. Pathogens and necrotic cells release factors that activate toll-like and other innate immune receptors that drive macrophage polarization toward the 'M1' proinflammatory macrophage. By contrast, the phagocytic uptake of apoptotic cells and other anti-inflammatory signals favors macrophage polarization toward anti-inflammatory or profibrotic 'M2' phenotypes. Fibrolytic macrophages release proteases which digest ECM.

**Table 1**
Types of macrophage activation and their related phenotypes.

| IFN-γ + PAMPs | DAMPs or LPS | IL-4 or IL-13 | IC + LPS | IL-10 or TGF-β |
|---|---|---|---|---|
| *Stimuli (evidence from in vitro studies)* | | | | |
| M1a<br>Classic type I inflammation | M1b<br>Innate inflammation | M2a<br>Alternative type II inflammation | M2b<br>Immunoregulatory | M2c<br>Immunosuppression |
| *Predominant phenotypic function in inflammation and repair processes* | | | | |
| Ingestion of pathogens, antigen presentation, complement synthesis, stimulation of Th1 cells | Ingestion of apoptotic cells | Recruitment of Th2 cells, eosinophils and basophils, killing of intracellular pathogens such as helminths | Promote Th2 responses, IgG class switching by B-cells, matrix synthesis | Resolution of inflammation, matrix synthesis and remodeling |
| *Inflammatory expression profile and determinants of polarization* | | | | |
| + regulation: STAT1/IRF5 CD40, CD80, CD86, MHC I and II, IL-1β, TNF-α, IL-6, -12, -15, -18, -23, iNOS, NO, ROS, CCL-2, -3, -5, -8, -15, -19, -20, CXCL-9, -10, -11, -13, MMPs<br>− regulation: scavenger receptors, TIMPs IL-4, -13, -10, TGF-β mTOR | + regulation: STAT1/IRF5 CD40, CD80, CD86, MHC II, IL-1β, TNF-α, IL-6, ROS, CCL2, 3, 5, CXCL9, 10, 11, scavenger receptor<br>− regulation: IL-12, IL-4, IL-13, IL-10, TGF-β mTOR | + regulation: STAT6/IRF4 PPARδ, PPRγ, KLF4, IGF-1, Arg1, CD40, CD80, CD86, MHC II, CCL2, 8, 13, 17, 26, CXCL9, 10, 11, 13, FIZZ1, YM1, scavenger receptor, mannose receptor, DC-SIGN, FcγR, IL-10, IL-1RA, IL-1RII, MMP12, TGF-β, mTOR, fibronectin<br>− regulation: IL-1β, IL-12, NO | + regulation: IL-10, CD40, CD80, CD86, MHC II, CXCL-3, CCL-1, -20, mTOR<br>− regulation: IL-12 secretion of modest amount of: IL-1β, IL-6, TNF-α | + regulation: STAT3, scavenger receptors A and B, IL-10, IL-1RA, TGF-β, mannose receptor, VEGF-C, PDGF, Arg-1, PGE2, FcγRs, CCR-1, -2, -5, CCL-16, -18, CXCL-4, -13, -23, SLAM, mTOR<br>− regulation: IL-1β, TNF-α, IL-6, -12 |

Depending upon the nature of the activating stimulus activated macrophages alter their expression of cytokines, costimulatory molecules and cytotoxic apparatus to promote the response to pathogens. M1-polarization, or classical activation, is induced by IFN-γ combined with microbial stimuli (PAMPs and DAMPs). M2-polarized macrophages have been classified into three groups: M2a, M2b and M2c. M2a macrophages (alternatively activated macrophages), are induced by IL-4 or IL-13 treatment. M2b macrophages arise upon stimulation with immune complexes. M2c macrophages (deactivated or regulatory macrophages), are anti-inflammatory macrophages generated by exposure to such stimuli as IL-10 or TGF-β. M1-polarized macrophages cross talk with Th1 and NK cells. M2 polarization of macrophages is driven by Th2 cells, basophils and eosinophils through their secretion of IL-4 or IL-13. M2b-like macrophages are polarized by interaction with B cells through antibody-/immune-complexes-mediated activation. M2c-like macrophages are polarized by interaction with Treg cells. Molecular pathways of macrophage polarization include activation of the transcription factors NF-κB (p65 and p50), AP-1, IRFs and STATs, which leads to the transcription of appropriate genes (cytokines, growth factors and surface molecules).

cells in injured tissues [88,89]. In vitro studies have classified alternatively-activated M2 macrophages into three subtypes: (1) M2a activated by IL-4 or IL-13, (2) M2b activated by immune complexes and LPS, and (3) M2c activated by IL-10 and TGF-β1 (Table 1). Generally, M2 macrophages express high levels of the mannose receptors, of scavenger receptor A as well as FIZZ1 and YM1. Furthermore, they produce CCL13, CCL8 or CCL26, which recruits eosinophils, basophils, and Th2 T cells, a program which derives from host defence against extracellular pathogens [90]. Experimental studies showed that direct IL-4/IL-10 treatment or genetically modified or transfused IL-10-stimulated macrophages help to resolve renal inflammation [91–94]. IL-10, which strongly activates M2c macrophages, was proposed to be a predominant cytokine that orchestrates the resolution of inflammation. Further evidence for this concept is provided by studies with tumor associated macrophages (TAMs), which create a non-inflammatory tumor environment. TAMs secrete large amounts of IL-10, VEGF and PDGF, which are necessary for angiogenesis and building the tumor stroma, conceptually like a chronic wound [95,96]. M2 macrophage injection into mice was protective in terms of inflammatory cytokine expression and accumulation of pro-inflammatory macrophages [93]. Also steroids suppress kidney inflammation by inducing anti-inflammatory macrophages [97]. However, depletion of anti-inflammatory M2 macrophage reduced muscle regeneration [21] as well as axonal regeneration after sterile spinal cord injury [98]. Similar positive effect of M2 macrophages on healing processes was observed during toxic CCl4-induced liver disease [99] and hepatic ischemia/reperfusion injury [100]. Moreover, macrophage depletion from sterile wounds not only delays wound healing but also leads to apoptosis of endothelial cells [81]. Thus, the switch to an anti-inflammatory macrophage phenotype supports the resolution of inflammation, a mandatory step for efficient tissue repair.

## 6. Monocytic phagocytes during tissue repair and fibrosis

Scarless wound healing occurs in lower animals even in non-sterile conditions. In mammals and even human fetuses it is limited to the sterile fetal environment or during childhood where tissue growth involves a higher density of tissue progenitors than in adults [101]. The process of scarring was evolutionarily conserved and is necessary to address the loss of tissues that cannot rapidly or only incompletely regenerate. Insufficient repair is associated with the persistence of alternatively-activated macrophages that continue to produce growth factors, which also stimulate fibroblast activation and ECM secretion [51]. For example, M2 macrophages secrete large amounts of transforming growth factor-β (TGF-β), a cytokine with anti-inflammatory as well as pro-fibrotic functions [95]. Other pro-fibrotic factors are CTGF, CCL17, CCL22, and Igf1. TGF-β is also up-regulated in epithelial cells that can no longer proliferate for repair and, therefore, produce TGF-β and CTGF to activate mesenchymal healing as a second line healing program [102]. In vitro, IL-4 and IL-13 induce STAT6 signaling to promote a macrophage phenotype that predominantly releases ECM molecules [42] and blocks inflammation [103]. Furthermore, arginase expressed by M2 macrophages can directly promote fibrogenesis by activating the synthesis of glutamate and proline which are necessary for collagen synthesis [104]. Macrophage-induced anti-inflammatory/pro-fibrotic responses occur inside solid organs following transient sterile inflammation, such as ischemia/reperfusion [72]. In the heart, macrophages orchestrate myocardial remodeling upon myocardial infarction [105]. For example after renal ischemia/reperfusion injury the phenotypic switch from pro-inflammatory toward anti-inflammatory macrophages is driven by tubular epithelial cell-derived factors as well as by the uptake of apoptotic neutrophils [72,106]. Progression of glomerulosclerosis and interstitial fibrosis in murine Alport syndrome of *collagen 4A3*-deficient mice is also associated with significant M2 macrophage infiltrates [107]. Therefore, blocking the recruitment and activation of pro-inflammatory macrophages, e.g. with CCL2 antagonist, remained ineffective in Alport syndrome as these cells do not contribute to the progression of renal scaring [108]. The same applies to hepatic fibrosis [109,110]. In contrast, blocking CCR1, a chemokine receptor also expressed by anti-inflammatory and pro-regeneratory M2 macrophages, reduced macrophages, subsequent fibrosis, and prolonged survival of *collagen 4A3*-deficient mice [111]. The pro-fibrotic role of CCR1+ interstitial macrophages was also confirmed in diabetic

nephropathy of db/db mice, adriamycin-induced nephropathy, and renal fibrosis after unilateral ureteral obstruction [112–116].

Another crucial population of immune macrophage-like immune cells that contributes to tissue repair is circulating fibrocytes [117]. Fibrocytes express the hematopoietic marker CD45 and the progenitor marker CD34 but they also secrete large amounts of collagen-1 [118]. Fibrocytes display a mixed phenotype between monocytic precursors and fibroblasts [119]. During inflammatory responses fibrocytes enter the tissue using surface CXCR4 receptor, which binds CXCL12 and participates in tissue repair [120]. Consequently, elevated CXCL12 levels were associated with accumulation of fibrocytes in patients with fibrotic lung disease [121], and the presence of these cells correlated with early mortality of patients with idiopathic pulmonary fibrosis [122]. In scleroderma patients, dermal fibrocyte numbers correlate with age and the stage of dermal fibrosis [123]. They seem to possess a unique ability to differentiate into fibroblasts and into myofibroblasts upon stimulation with TGF-β [124–126]. More recently, it has been shown that also CXCR3+ hematopoietic cells might be the subset responsible for scar formation/fibrosis [127].

Together, macrophages contribute to tissue fibrosis only because they support a mesenchymal healing response that is activated once epithelial/parenchymal repair remains insufficient. This is driven by a microenvironment of apoptotic cells and growth factors that drive macrophages to themselves produce pro-fibrotic mediators. In chronic disorders, especially in diffuse injuries, the process of fibrosis then accompanies the progressive loss of function, which largely depends on the loss of parenchyma. However, sclerosis, the functional consequence of fibrosis, can contribute to disease progression, e.g. the stiffening of the cardiac ventricles or of the vascular wall.

## 7. Monocytic phagocytes during the resolution of fibrosis

Distinct macrophage populations also limit or even reverse tissue fibrosis by digesting ECM deposits. Two proteolytic cascades, the matrix metalloproteinases (MMPs) and their endogenous inhibitors (the tissue inhibitors of metalloproteinases-TIMPs, the plasminogen activators uPA and tPA, and the plasminogen activator inhibitors-PAIs), regulate matrix turnover [128,129]. However, the role of MMPs in fibrosis is complex and seems to be compartment, – time – and cell type-specific. The in vivo effects remain difficult to predict because MMPs also cleave and activate a variety of cytokines. Several studies suggest an increase in MMP expression, rather than a loss of MMPs, during fibrosis [130,131]. For example, MMP-2, MMP-7 and MMP-9 were elevated in experimental models of lung fibrosis and their overexpression was shown to promote fibrogenesis [132–134]. They are most probably involved in basement membrane digestion, which leads to a loss of structural integrity and contributes to parenchymal damage and dysfunction. Furthermore, *Mmp7*-deficient mice are protected from bleomycin-induced fibrosis [132]. However, when macrophages are depleted in the late phase of toxic liver fibrosis the clearance of liver scars is delayed, because scar-associated macrophages no longer release MMP13, which breaks down ECM [135]. Various MMPs have been implicated in the severity of inflammation and fibrosis in asbestos-induced lung injury and MMP blockade attenuated inflammation and fibrosis [136]. For example, pirfenidone, an anti-fibrotic agent that decreases collagen deposition in a variety of animal models and humans is believed to modulate MMP activity [137]. In some experimental models, pirfenidone reduced the expression of TIMP-1, MMP-2 and MMP-9 but not of MMP-13, which was associated to less TGF-β1 expression [137–139]. Macrophages also release MMP2 and MMP9 that degrade collagen in the kidney [140,141]. Interestingly, late onset of MMP inhibition in mice with progressive renal scaring aggravated renal fibrosis, while it was protective during the early stage of the disease [142]. It seems that certain MMPs do not only degrade collagen but also rather digest ECM including basement membranes, which compromises the integrity of epithelial compartments [143]. ECM breakdown also produces small ECM peptides and glycosaminoglycans, which themselves can act as immunostimulatory DAMPs and potentiate tissue inflammation [144]. Fibrolytic macrophages have such an excessive fibrolytic activity but their phenotype has not yet been clearly defined, e.g. by their specific surface marker expression profile. Recent studies showed that treatment of cultured macrophages with M-CSF, but not GM-CSF, shifts macrophages from antigen-presenting cells to subpopulation of IL-10-producing suppressor cells [145]. IL-10 has immunosuppressive function, which acts on macrophages and prevents them from production of proinflammatory cytokines, and to downregulate expression of co-stimulatory molecules in a STAT3-dependent manner [146–148]. Moreover, IL-10 produced by suppressor macrophages prevents the development of Th1-type and Th2 T-cell responses, and promotes the differentiation of T cells to regulatory T-cell population [149]. Also proinflammatory factors such as IFN-γ or IL-12 may induce regulatory macrophage population. Various studies demonstrated that continuous exposure of macrophages to TLR2, TLR4 or TLR9 ligands leads to development of immunosuppressive state [150–152].

Latest studies identified also non-proteolytic and antifibrotic factors such as BMP7. BMP7 is one of over 20 known members of BMP family that are structurally and functionally related and are part of TGF superfamily of cytokines [153]. BMP7 is indispensable for normal kidney development [154]. However, unlike TGF-β, BMP7 was found to be downregulated in experimental and human fibrosis [28,155]. Furthermore, the kidney mesenchymal cells of BMP7 null embryos were not able to differentiate [156]. Other studies have demonstrated that BMP7 protects the kidney from injury by enhancing the survival ability of tubular cells and reduction of inflammation [157,158]. Therefore, BMP7 might be a crucial survival and differentiation factor for kidney mesenchymal cells.

Taken together, macrophages already contribute to the breakdown and turnover of ECM during homeostasis but this property becomes more prominent in the microenvironment of scar tissue. Removing fibrous tissue is the final phase of the wound healing process. Activating the fibrolytic properties of these macrophages may be another option to reverse tissue fibrosis. Such fibrolytic macrophage populations have been described in some organs but deserve further phenotypic characterization.

## 8. Summary

Tissue mononuclear phagocytes can display a phenotype of resident dendritic cells or of resident macrophages, but they are important for maintaining homeostasis. During tissue injury changing tissue environments shape the phenotype of these mononuclear phagocytes to provide them with additional functional properties that meet the tissues' need to address the danger. It is instrumental to apply the model of (dermal) wound healing upon traumatic injury to better understand their role in each of the phases of danger control and tissue repair also in other organs. Accordingly, pro-inflammatory (M1) macrophages support host defense by enhancing the inflammatory environment even in sterile tissue injuries. The inflammatory response following tissue injury has important roles in both normal and pathological healing. Immediately after injury, the innate immune system is activated and is responsible for recruitment of inflammatory cells from the circulation. Local, resident immune cells, including macrophages produce chemoattractans that enhance inflammatory responses by recruiting more leukocytes. Understanding of macrophage population switch and mechanisms which regulate macrophage function seems to be an attractive therapeutic target, both to reduce fibrosis and scarring, and to improve healing of chronic wounds. It seems that during normal inflammation, which includes mast cell degranulation and neutrophil infiltration, macrophages have an important balancing role. Thus, the role of macrophages must always be considered in the context of the specific environment.

Anti-inflammatory macrophages support the resolution of inflammation. This process involves the expression of growth factors that promote parenchymal repair, which includes mesenchymal repair. For example, the anti-inflammatory cytokine TGF-β1 is a potent pro-fibrotic cytokine that activates mesenchymal repair mechanisms.

Finally, macrophages contribute to the removal of fibrous tissue. Mediating the resolution phase of healing includes capillary regression and collagen remodeling. Macrophages can produce factors that terminate the repair response. However, little is known about how a particular population of macrophages terminates the healing response but the agent modulating the phenotype of these particular macrophages or ex-vivo production of such cells possesses great therapeutic potential. Furthermore, using single macrophage factors as therapeutics raise difficulties with optimum delivery systems, timing and concentration, not to mention the proteolytic condition which limits the half-life of therapeutic agents. One alternative would be in situ activation, recruitment or addition of exogenous macrophages which are source of beneficial growth factors and cytokines that stimulate regeneration of damaged tissue, angiogenesis and actively leads to resolution of established fibrosis. However, increasing the number of macrophages in the fibrotic tissue might imbalance the environment and macrophages might switch again the phenotype and potentiate inappropriate conditions such as inflammation instead of resolution of fibrotic tissue or regeneration. The strategy of driving macrophages within tissue toward a suppressor phenotype might be a promising therapeutic approach opening a novel area of cell-based medicinal products.

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